PRESENT STATUS OF ANTIBIOTIC THERAPY IN VIRAL AND RICKETTSIAL DISEASE*

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WE will begin with a discussion of the rickettsial diseases of man even though these are of appreciably less medical importance in New York and in the United States than are the viral diseases. Within the past three years the problem of the treatment of the rickettsial diseases has been solved. When one speaks of the recent advances and the present status of the therapeutic control of these infections, he speaks of the use of the antibiotics chloramphenicol, aureomycin and terramycin. While this subject is relatively new, several rather complete reviews have already been published.[1,2] Therefore, it will not be necessary at this time to recount the amazing story of the successful search for these substances, the extensive laboratory experience which foretold the efficacy of these drugs in patients, nor the details of the early clinical trials.

In discussing the rickettsioses, it appears preferable to select one of these formerly notorious diseases and to summarize the present information about its treatment. This is feasible because the rickettsial group of agents, and the illnesses which they induce, are similarly affected by the three new antibiotics which have now come into wide usage. Those instances in which minor differences are encountered in the therapy of the diseases will be disposed of briefly.

Scrub typhus will be taken as the illustrative example of the present status of the treatment of rickettsial infections. There are several reasons for this. While not the first of the rickettsioses to be subjected to the newer antibiotics, it was the first in which one of the newer methods of treatment was carefully evaluated. Furthermore, it remains the rickettsial disease which has been most extensively studied by a single group of investigators, hence, the observations of this group on the comparative efficacy of the different antibiotics are of particular

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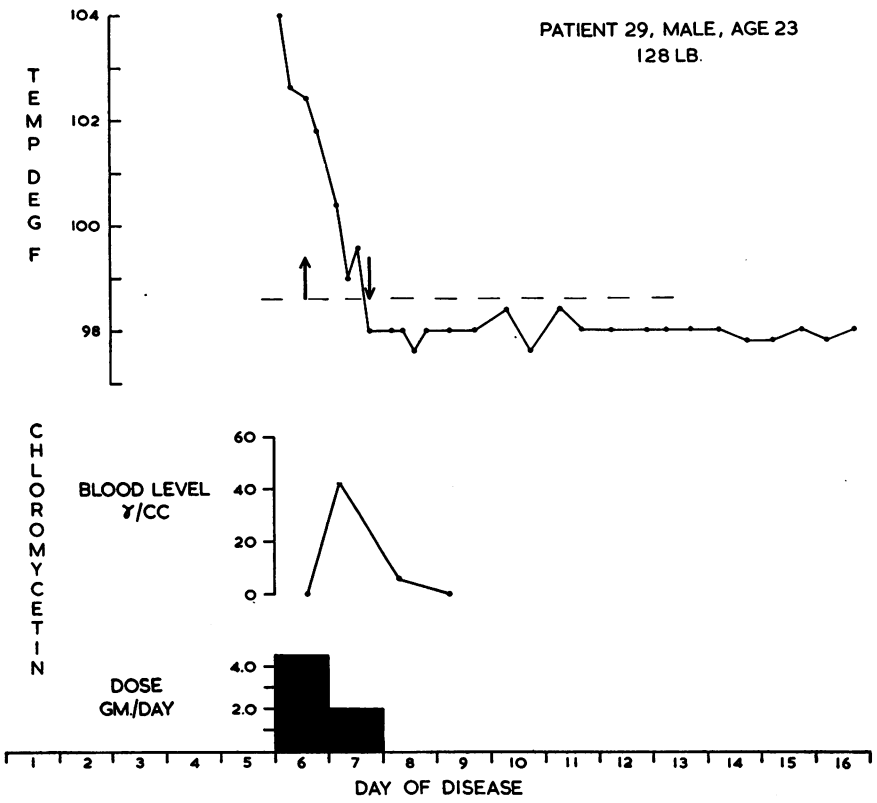

Figure 1—Clinical course of scrub typhus in a Malayan treated with chloramphenicol. (Reproduced by permission of the Journal of Clinical Investigation, 1949, *28*:1202.)

value. Finally, my own observations in this field have been more closely associated with scrub typhus than with the other rickettsial diseases.

Figure 1 illustrates the clinical course of disease in a Malayan patient with scrub typhus who was treated with chloramphenicol. A total of about 6.0 grams of drug was administered orally over a period of 24 hours. Before the end of this course of antibiotic, the patient was afebrile and markedly improved. Convalescence was uneventful.

TABLE 1—SCRUB TYPHUS PATIENTS TREATED WITH CHLORAMPENICOL, AUREOMYCIN, TERRAMYCIN OR PARA-AMINOBENZOIC ACID

Therapy	*No. of Patients*	*Average Duration of Fever after Treatment (hrs.)*	*Fatalities*
Chloramphenicol	100	31	0
Aureomycin	29	25	0
Terramycin	7	47	0
Paba	15	89	0
		Duration of Disease	
None	19	17 Days	1

Table 1 summarizes the three year collaborative experience of the U. S. Army Medical Research Units and the members of the Institute for Medical Research in the treatment of patients with scrub typhus.[3] One hundred of these received chloramphenicol; the average duration of their fever after beginning therapy was thirty-one hours. Twenty-nine patients were treated with aureomycin and they became afebrile after twenty-five hours. Seven other patients were treated with terramycin and their fever persisted on the average for forty-seven hours. The figure also contains information on the results obtained in fifteen patients who were treated with para-aminobenzoic acid; here almost ninety hours elapsed from the time the drug was started until the patients were fever free. During the course of these studies in Malaya, there were nineteen patients with scrub typhus who received only symptomatic treatment. These were cared for at a time when specific therapy was not available or else were first seen late in their illness at a time when they did not appear dangerously sick. It may be noted that the average duration of fever in these nineteen control patients was seventeen days. No deaths occurred among the 151 treated cases while one of the nineteen controls succumbed with scrub typhus. The mortality in this disease, in untreated patients, varies considerably in different geographic areas. In Malaya, where these studies were made, the mortality is about 5 per cent.

Such data as those provided in Table 1 clearly show that the three new antibiotics, namely, chloramphenicol, aureomycin and terramycin, are far superior to para-aminobenzoic acid, which was the only useful specific remedy available prior to the advent of chloramphenicol. The

therapeutic effects of aureomycin in patients with scrub typhus are as excellent as those obtained with chloramphenicol. Certain of the patients who received terramycin responded as well as would have been expected had they been given either chloramphenicol or aureomycin. However, a few of those who received terramycin were a little slow in responding and these raised the average febrile period for the group to forty-odd hours.

The Malayan experience revealed practically no serious side effects attributable to the use of chloramphenicol in patients with scrub typhus. While no serious untoward manifestations were exhibited by those persons who were given aureomycin, about 20 per cent of them had annoying gastrointestinal irritation; however, in no instance was it necessary to discontinue aureomycin because of these side effects. In contrast the incidence of nausea and vomiting in the Malayan patients who received terramycin was appreciably greater than in those who were given the other two drugs. Indeed, in several instances these manifestations were sufficient to warrant transferring the patients from terramycin to one of the other two antibiotics. This experience with terramycin is somewhat in contrast with the observations of others and may have been dependent upon several factors. In the first place, the Malayan patients were given relatively large doses of terramycin, i.e., a regimen similar to that used with chloramphenicol, and in the second place, early production lots of this antibiotic were employed. Subsequently, more highly purified lots of terramycin were administered by others for research purposes and were distributed commercially.

Each of the therapeutic agents listed in Table 1 has a marked capacity to inhibit the growth of rickettsiae but none is capable of eliminating the rickettsiae from the patient's tissues. Therefore, these drugs are rickettsiostatic, not rickettsiocidal. It is important to remember this point for it has a strong bearing on the method by which the treated patient ultimately recovers from his rickettsial disease and it also bears on the duration of therapy which is required to prevent a relapse.

The specific antibiotics control the manifestations of rickettsial infection by suppressing growth of the agent and enable the patient to cure himself. Thus, eventual recovery in the treated, as well as in the untreated, patient depends upon the development of immunity and the control of the rickettsiae by this mechanism. Patients with scrub

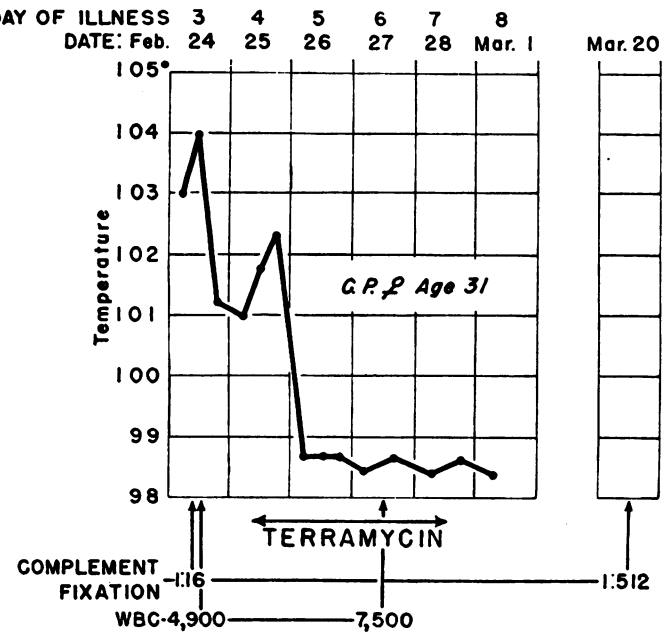

Figure 2—Patient with rickettsialpox who was treated with terramycin. (Reproduced by permission from *Ann. N. Y. Acad. Sci.*, 1950, reference 4.)

typhus who were treated with either chloramphenicol or aureomycin for a period of twenty-four hours were able to suppress the clinical manifestations of their illness for a period of about one week. If immunity had not developed by the time this suppressive effect had begun to diminish, then recrudescence of the disease occurred. Therefore, a proportion of those patients who were treated for a short time within the first few days after onset suffered relapses; incidentally, such relapses were readily controlled, or prevented, by additional therapy. In contrast, patients who were treated during the second week for a similar short period of time did not suffer relapses. These persons were gaining immunity as the suppressive effect of the antibiotic waned, hence, control of the disease passed from one mechanism to the other without a break in continuity and no relapses occurred.

The other rickettsial diseases are benefited about as much by the newer antibiotics as is scrub typhus. Patients with epidemic or murine typhus become afebrile within about two days after therapy is instituted while those with Rocky Mountain spotted fever require approximately three days. Patients with rickettsialpox generally recover promptly and

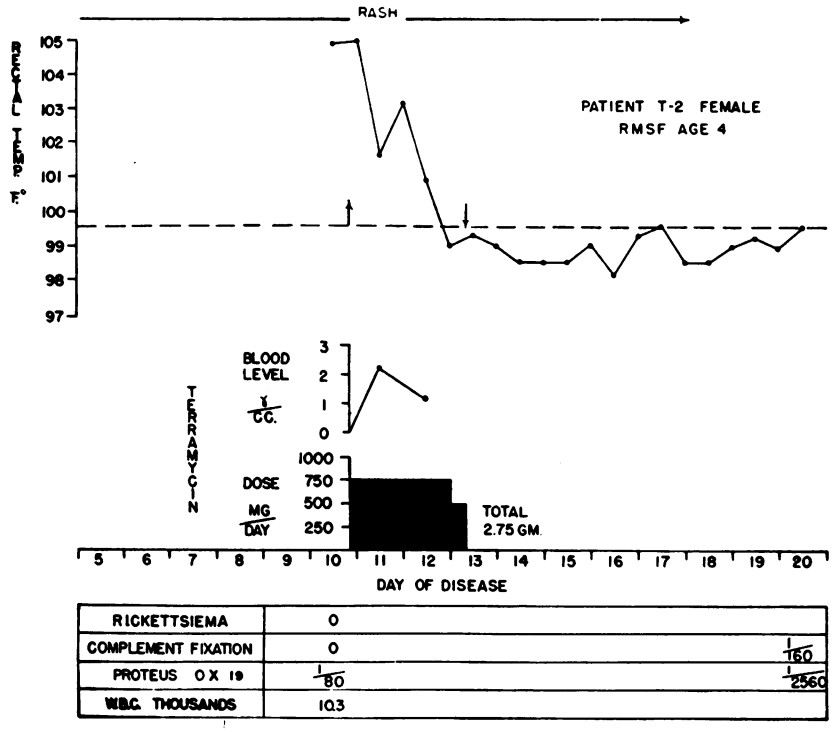

Figure 3—Terramycin in patient with Rocky Mountain spotted fever.
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patients with Q fever are materially benefited by these therapeutic agents. While there is no need to discuss in detail the use of each of these three antibiotics in these various rickettsial diseases, it is of interest to illustrate certain of the clinical results obtained in several of them with the newest member of the group, namely, terramycin.

Figure 2 illustrates the prompt therapeutic response obtained in a patient with rickettsialpox who was treated with terramycin. This woman was cared for by Dr. Harry Rose and the graph is taken from one of his recent publications.[4]

Figure 3 summarizes the results obtained in one of Dr. Woodward's patients who received terramycin for the treatment of Rocky Mountain spotted fever.[5] The chart is essentially identical with earlier ones which portrayed the effect of chloramphenicol and aureomycin on patients with this disease.

The physician who has either chloramphenicol, aureomycin, or terramycin can treat the rickettsial diseases of man and expect to get

dramatic and gratifying results. Our experience has led us to prefer these three in the order just listed. However, that is the opinion of one group and others, for example, Ruiz Sanchez in Mexico, prefer aureomycin to chloramphenicol.[6] The truth of the matter is that all three are so efficacious in the rickettsioses that it is rather difficult to choose between them. We are indeed fortunate in having three drugs which are so excellent.

The matter of drug dosage for the rickettsioses is relatively simple. The administration of 3.0 grams orally each day until the patient's temperature is normal is a good general rule to follow. When one uses chloramphenicol, a loading dose of 3.0 grams is usually employed. With aureomycin or terramycin the loading dose is sometimes omitted and the total daily dose may be reduced slightly. There is no real indication for continuing treatment after the patient becomes afebrile; if a recrudescence of disease should occur, another course of drug may be given. There seems to be no evidence of the development of drug resistance which would interfere with the efficacy of the antibotic in the treatment of a rickettsial relapse.

There is no doubt that continuing efforts will be made to discover new drugs and antibiotics which are of value in the treatment of the rickettsial diseases. While this is to be encouraged to some extent, it should be realized that such efforts have much in common with gilding the lily. The recent great advances in the treatment of rickettsial diseases are on a par with the giant forward strides which were taken with the application of the sulfonamides and penicillin to the treatment of bacterial diseases. The one important step which remains in the therapy of rickettsial diseases is the discovery of a truly rickettsiocidal drug which is non-toxic for man. If such were found, it would probably supersede the present rickettsiostatic substances. It is my personal opinion that the advances in the treatment of the rickettsioses have been so great that research efforts can now be diverted from these diseases to the important subject of the therapy of viral diseases.

Now that we are ready to discuss the problem of therapy of viral diseases, I wish that I had the facile adaptability of the Roman mythological figure Janus who could face two ways at the same time. Viruses of psittacosis-lymphogranuloma venereum group are rather closely related to the rickettsiae and are highly susceptible to the new rickettsiostatic agents. When one proceeds from this group to the remaining viral

agents, he arrives on rather insecure ground. In this last segment of the field, laboratory experiments which indicate efficacy of the antibiotics against the viral agents are either lacking or have given conclusively negative results. Hence, in discussing the use of modern therapeutic methods in the treatment of many of the viral diseases, one is dependent upon the evaluation of the clinical response of patients with a disease which is often of variable severity and irregular duration and is frequently complicated by bacterial infection. It need hardly be mentioned that this part of the field is a quagmire which demands cautious treading.

Reports have appeared on only a few patients with psittacosis or ornithosis who have been treated with chloramphenicol or aureomycin. The results in these instances were as encouraging as one would have anticipated on the basis of the excellent therapeutic effects of these antibiotics in experimental infections with psittacosis viruses. Aureomycin and chloramphenicol appear to be of considerable value in the treatment of patients infected with the virus of lymphogranuloma venereum. Furthermore, the evidence to date suggests that these antibiotics are superior to the sulfa drugs. It is worth noting that the recent reports of Greenblatt[7] and others have confirmed the initial studies of Wright and Sanders[8] regarding the marked and rapid improvement of lymphogranulomatous proctitis following therapy. The workers in Georgia[7] are not as enthusiastic as earlier investigators on the subject of relief of the bubonic form of lymphogranuloma venereum; furthermore, they are of the opinion that aureomycin is somewhat superior to chloramphenicol for treating this disease.

The viruses which cause trachoma and inclusion blennorrhea have certain points in common with members of the psittacosis-lymphogranuloma venereum group; these include similar morphological properties as well as susceptibility to the sulfonamides. Both aureomycin and chloramphenicol have been reported to be of great value in the treatment of these infections of the eye. Freyche[9] in an excellent recent summary of the treatment of trachoma concludes: "aureomycin and chloramphenicol . . . on both theoretical . . . and practical . . . grounds may constitute the specific therapeutic agent or agents for this disease." It may be noted that in most cases reported to date (and these are less than 100), the antibiotics have been applied locally to the eye. However, in the few patients who have received aureomycin systemically and in the

somewhat large number who have received chloramphenicol by mouth[10] the results have been sufficiently gratifying to warrant more extensive studies. Investigations on the use of the new antibiotics in the treatment of trachoma are now in progress on a considerable scale in several widely separated geographic areas of the world.

There are a number of virus infections with dermatological manifestations which have been subjected to treatment with chloramphenicol and aureomycin mainly on the grounds that these therapeutic agents might help and would do no harm. These diseases include herpes zoster, extensive involvement with herpes simplex virus, widespread eczema complicated by infection with vaccine virus, molluscum contagiosum and a number of other conditions which bear the impressive nomenclature so dear to the dermatologists. I wish it were possible to give you a simple answer as to whether these therapeutic regimens are worthwhile. Frankly, it is impossible to evaluate the reports at this time. It is well to remember that the newer antibiotics are potent antibacterial agents active against a wide variety of micro-organisms; the antibacterial effects may have contributed to the improvement in the patient's condition which was attributed to the therapy. While it is not possible on scientific grounds to approve the use of aureomycin, chloramphenicol, terramycin, or penicillin in these dermatological infections of viral origin, nevertheless, as a physician I feel justified in employing one or another for at least a few days. If no benefit is derived within this period, then one may abandon the antibiotics with a clear conscience.

A considerable number of reports have appeared on the treatment of primary atypical pneumonia and of influenza of either the pure viral type or complicated by pneumonia. Most of these have recorded rather prompt improvement in the patient's condition. In the viral infections of the pulmonary tissue, as in the viral infections of the skin, it is extremely difficult to divorce the viral and bacterial elements and, as a corollary, it is almost impossible to decide whether the beneficial effects attributed to the newer antibiotics were dependent upon their antibacterial effect or their action on the viral agent. Aureomycin, chloramphenicol and terramycin are of great value in the treatment of bacterial pneumonia. Too often the diagnosis of primary atypical pneumonia is made on no grounds other than the fact that the patient with pulmonary consolidation fails to respond promptly to penicillin therapy. It could be that many of the instances in which the three new anti-

biotics succeeded when penicillin failed were dependent upon their antibacterial effect rather than on the antiviral action. On the other hand, there are a number of groups of investigators who have considered these newer antibiotics to be valuable in the treatment of patients with the usual clinical findings of primary atypical pneumonia associated with a rise in cold agglutinin substances and without conspicuous evidence of bacterial infection.[11] The physician who sees such patients is justified in employing therapeutic amounts of the newer antibiotics. However, if the selected drug does not elicit definite improvement within two days, there is little indication for continuing it.

The problem of the therapy of influenza is perhaps more difficult to evaluate than that of atypical pneumonia. The simple viral infection without pulmonary consolidation, as generally seen in recent years, is a relatively mild disease which requires only rest and symptomatic therapy. Those patients who develop pulmonary consolidation surely warrant treatment with the antibacterial substances. It may be mentioned in passing that none of the chemotherapeutic or antibiotic agents now available have any appreciable activity against influenza viruses in experimental animals.

In this connection it is worth-while bringing to your attention the experience with influenza in the Canadian Arctic last year. On Victoria Island, fatal influenza, resembling that seen in the last great pandemic, attacked a number of small isolated groups of Eskimos.[12] Some sixteen deaths occurred among the ninety Eskimos, all of whom contracted the disease, before a medical team was flown in to care for the patients. With the arrival of the team, practically all patients were treated with penicillin and the fatalities ceased abruptly, although a number of the patients had pneumonia when therapy was instituted. Subsequent studies on the viruses which were isolated from one of the fatal cases as well as from several survivors showed that the strains of virus were essentially identical with certain of the influenza A and A prime strains which had caused mild disease in more populated areas within recent years.[13] It would appear that this Arctic experience demonstrated the importance of modern chemotherapy in controlling the bacterial element in fatal cases of epidemic influenza. It is not too much to hope that this observation in the Arctic may provide a preview of the usefulness of the antibiotics in preventing deaths in the next pandemic of influenza if or when it occurs.

In summary, the treatment of rickettsial diseases has been revolutionized within the past several years by the introduction of the highly specific rickettsiostatic antibiotics chloramphenicol, aureomycin and terramycin. These same antibiotics possess specific activity against viruses of the psittacosis-lymphogranuloma venereum group which are not too distantly related to the rickettsiae. Practically all of the other viral agents which have been studied in the laboratory are unaffected by the chemotherapeutic and antibiotic agents which are now available. While the human diseases caused by certain of these viruses appear to be benefited by antibiotics, it is difficult to evaluate these results. In a number of such instances, however, the use of the antibiotics is warranted, even though the academic question of their mode of action remains unanswered.

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